REVIEW

Kinase inhibitors for advanced medullary thyroid carcinoma

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The recent availability of molecular targeted therapies leads to a reconsideration of the treatment strategy for patients with distant metastases from medullary thyroid carcinoma. In patients with progressive disease, treatment with kinase inhibitors should be offered.

KEYWORDS: Thyroid Neoplasms; Molecular Targeted Therapy.

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INTRODUCTION

Medullary thyroid carcinoma (MTC) accounts for 5–8% of all thyroid cancers (1,2). Distant metastases are observed at presentation in 7–23% of MTC patients. In patients with elevated calcitonin levels after initial treatment, clinical recurrence will occur at different time intervals after surgery, depending on the amount of persistent disease and the progression rate. Recurrent disease in the neck and mediastinum is frequently amenable to surgery, and some patients may also benefit from external radiation therapy. Distant metastases are the main cause of MTC-related death. They often affect multiple organs, including lungs, bones, and liver, and more rarely brain, skin, and breast, and they are frequently associated with a neck recurrence (3). In patients with recurrent disease, a good quality of life is usually maintained, but diarrhea may be debilitating. Slow tumor growth is common and, in retrospective series, survival after the discovery of distant metastases was around 25% at 5 years and 10% at 10 years, but recent series suggest that survival rates might be higher with earlier discovery of metastatic disease.

Selection of patients for clinical trials

Patients with metastatic MTC must be accurately characterized concerning all clinical prognostic indicators, including age, performance status, histology, disease extent and location, and progression rate. The importance of this latter parameter cannot be overemphasized, as many patients with metastatic MTC can be asymptomatically stable for long periods of time, and in such patients, the benefits of novel therapies may be largely outweighed by drug toxicities and the rigors of clinical trial participation. Also, there is no evidence that the efficacy of these novel therapies is higher at an early stage than later when metastases are larger in size, and treatment can be postponed in most patients until progression has been documented by imaging.

Imaging should emphasize identification of all clinically relevant sites of disease, including tumors large enough to be serially assessed to determine response to therapy as well as those that might require additional localized intervention, such as surgery, external radiation therapy, radiofrequency ablation, cryotherapy, cement injection, or embolization. These treatments should be performed whenever needed before the initiation of any systemic treatment, and they may enable systemic treatment to be postponed in some patients.

Diagnostic procedures in metastatic MTC patients should include spiral computed tomographic scanning or magnetic resonance imaging of the brain, ultrasonography of the neck, contrast-enhanced spiral computed tomographic scanning of the neck and chest, triple-phase computed tomographic scanning or preferably magnetic resonance imaging of the liver (because liver metastases may be difficult to visualize with computed tomography during anti-angiogenic treatment), bone scintigraphy and magnetic resonance imaging of the spine and pelvis. Fluorodeoxyglucose (FDG) uptake on positron emission tomography scanning is usually low, and for this reason FDG positron emission tomography scanning is usually poorly sensitive and cannot be used to assess progression rate or response to treatment (1,3).

In the absence of treatment, imaging is repeated every six months, and progression rate is assessed using Response Evaluation Criteria in Solid Tumor (RECIST) (4,5). Patients with measurable lesions and documented progression in a

given time interval (between 6 and 15 months) should be considered candidates for systemic treatment. Progression rate can also be evaluated by the doubling times of serum markers, calcitonin and carcinoembryonic antigen levels (6,7), but progression should always be confirmed by imaging (4,5).

Standard Systemic Treatments

Symptomatic treatments of diarrhea include loperamide, diphenoxylate/atropine, and codeine (1). Earlier clinical trials of cytotoxic chemotherapies suffered many shortcomings. Due to both the rarity of apparent benefit and the significant toxicity of the treatments, physicians enrolled only patients with a large tumor burden and rapidly progressive metastatic disease. The few prospective trials that were reported did not include sufficient numbers of patients to demonstrate benefits or reject false-negative conclusions. None used the now-standard RECIST (4,5), and many trials reported results mixing together patients with differentiated thyroid cancer, MTC and anaplastic thyroid cancer. The most frequently tested agent in thyroid cancer patients is doxorubicin, used either alone or in combination with cisplatin. Tumor response rates range from 0% to 22% in MTC patients, with all responses being partial and only lasting a few months (8,9). As MTC is a well-differentiated endocrine tumor, various combinations of 5'-fluorouracil, dacarbazine, streptozocin, cyclophosphamide, and vincristine have been used and produced some responses (in about 20% of patients) with symptomatic improvement in some (10). Newer cytotoxic drugs, such as taxanes, gemcitabine, or irinotecan, have not been reported in significant series of MTC patients.

Treatment with bi-specific antibodies directed against carcinoembryonic antigen and diethylene triamine pentaacetic acid (DTPA) and with DTPA labeled with ^{13}I or with octreotide labeled with yttrium-90 prolonged overall survival but did not induce objective responses in patients with large metastases (11,12), and hematological and renal toxicities were significant. Interferon α and somatostatin analogs used either alone or in combination in MTC patients only produced an inconstant and transient effect on diarrhea. Dendritic cell immunotherapy may be effective but is still under evaluation (13).

In conclusion, these therapeutic methods provide low response rates in patients with advanced and progressive refractory MTC.

Molecular Targeted Therapies

Several molecular abnormalities thought to be important in thyroid oncogenesis and/or progression have been defined in MTC and represent potential targets for therapy (1,2,14). The aims of treatments are first to improve the quality of life and second to prolong overall survival. Because it is difficult to demonstrate an improvement in overall survival in patients with slowly progressing disease and a long life expectancy, surrogate parameters have been used: the response rate studied in phase II trials is poorly related to overall survival; progression-free survival studied in randomized phase III trials is better related to overall survival. At the present time, results of only one phase III trial are available.

Molecular targets

In most familial forms of MTC, one of a variety of germline RET (rearranged during transfection) mutations is found. The proto-oncogene receptor RET is a membrane receptor with tyrosine kinase activity, and these mutations activate the kinase function that triggers downstream mitogenic and survival signaling. Somatic mutations in RET are also found in 30–50% of sporadic MTC tumors, and of these, 80% are mutations at codon 918. Once activated, RET stimulates several intracellular signaling cascades that include the GTPase-Ras/serine/threonine-protein kinase B-raf (BRAF)/mitogen-activated protein kinase (MAPK) and the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/alpha serine/threonine-protein kinase (AKT) pathways. Besides RET, BRAF mutations have only been rarely reported in MTC, but RAS mutations have been found in 68% of MTC tumors without RET mutation and rarely in MTC harboring a RET mutation (15). Finally, little is known about loss of function of tumor suppressors in MTC (1,2).

Angiogenesis serves a critical role in the development of these hypervascularized tumors and provides another set of potential molecular targets for therapy. Vascular endothelial growth factors (VEGF) and VEGF receptors (VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1, KDR)) are often overexpressed in thyroid cancer tissues, both in tumor cells and supporting vascular endothelium, and they also trigger the MAPK signaling pathway (17). Receptors for the fibroblast growth factor and for the platelet-derived growth factor are also often overexpressed and may play a role in tumor angiogenesis.

Table 1 - Kinase inhibitor activities relevant to thyroid carcinomas.

Drug	Inhibitory Concentration 50% (nm)					
	VEGFR1	VEGFR2	VEGFR3	RET	BRAF	Other targets
Axitinib	1.2	0.25	0.29			
Sunitinib	2	9	17	41		
Motesanib	2	3	6	59		PDGFR, CKIT
Sorafenib		90	20	49	6	
Vandetanib		40	110	100		EGFR
Pazopanib	10	30	47			PDGFR, C-KIT
Cabozantinib (XL184)		0.035		4		C-MET, C-KIT
Lenvatinib (E7080)	22	4	5	35		PDGFR, FGFR

VEGFR1 = vascular endothelial growth factor 1, VEGFR2 = vascular endothelial growth factor 2, VEGFR3 = vascular endothelial growth factor 3, BRAF = GTPase-Ras/serine/threonine-protein kinase B-raf.

Molecular targeted therapies used in thyroid cancer

The RET kinase appears to be a promising target for molecular therapy of MTC (2,14). ATP-competitive inhibitors that exert an inhibitory effect on the RET kinase prevent the activation of the downstream proteins (Table 1). Owing to the close structural relationship between the kinases in RET and VEGFR, most VEGFR kinases inhibitors also inhibit RET kinase. For example, vandetanib effectively inhibits VEGFR2, VEGFR3, epidermal growth factor receptor (EGFR) and RET kinases. X-ray crystallographic analysis of the vandetanib-RET kinase complex demonstrates that the drug docks into the ATP-binding pocket of the kinase, inhibiting the wild-type enzyme and most of the activated mutant forms. Sorafenib, sunitinib, motesanib, lenvatinib (E7080), and cabozantinib (XL-184) are also multi-kinase inhibitors that share the ability to inhibit RET and VEGFR, along with other kinases; in contrast, axitinib and pazopanib seem to act only as anti-VEGFR agents. C-met is overexpressed in medullary thyroid cancer as a result of RET activation, and cabozantinib that inhibits both RET and c-met is being tested in MTC (16,18).

Results of clinical trials

Available results in MTC (Table 2) patients from phase I, II, and III trials have clearly confirmed the efficacy of these compounds. To date only vandetanib has achieved US Food and Drug Administration regulatory approval and more recently European Medicines Agency approval for therapy of advanced and progressive MTC, but some treatment guidelines recommend use of available agents for selected patients with progressive metastatic disease on the basis of the phase II results (1,19).

Vandetanib at the maximal tolerated dose (300 mg/day) included 30 patients with hereditary MTC who had germline RET mutations. Partial response was observed in 10 patients, among whom six had a confirmed partial response, and stable disease longer than 24 weeks was observed in another 16 patients (20). Another phase II trial with vandetanib (100 mg/day) included 19 hereditary MTC patients, and a partial response was observed in three patients and stable disease lasting 24 weeks or longer in a further 10 patients, demonstrating anti-tumor activity in this setting. However, it is not clear whether the lower dose induced less toxicity, and two patients discontinued the study because of a vandetanib-related adverse event (21).

A large randomized phase III trial comparing progression-free survival (PFS) in patients treated with vandetanib (300 mg/day) or placebo has been completed on 331 patients with locally advanced or metastatic MTC (22). The median PFS was significantly prolonged from 19.3 months in the placebo arm to a predicted median of >30.5 months (median not yet reached) in the vandetanib arm (Hazard Ratio 0.46; $p<10^{-4}$); partial responses were observed in 45% of patients treated with vandetanib, with a predicted median duration of response of 22 months. Benefits of vandetanib treatment were observed in all subgroups of patients, regardless of RET mutation status, progression rate and tumor burden. Sufficient events to analyze overall survival have not occurred yet. The serum calcitonin and carcinoembryonic antigen levels decreased by ≥50% and over a minimum of four weeks in 69% and 52% of patients, respectively. However, calcitonin production by MTC is controlled by the RET signalling pathway, and RET kinase inhibitors may decrease calcitonin production independent of tumor mass changes (23). Time to worsening of pain was significantly improved by vandetanib. In some patients, diarrhea was improved rapidly after initiation of therapy, and this often allowed patients to resume a normal social life. Adverse events, including diarrhea, fatigue, rash, hypertension, and prolongation of the QTc interval on electrocardiogram, were mainly classified as grade 1 or 2. However, 12% of patients receiving vandetanib discontinued treatment and 35% required that their dose of vandetanib be reduced because of an adverse event.

Cabozantinib (XL-184). In a phase I trial, cabozantinib induced a partial response in 17 of 34 evaluable MTC patients, of whom 10 had a confirmed partial response, and another 15 patients had stable disease (18). Partial responses were observed regardless of RET mutation status, and in both treatment-naïve patients and patients who had previously been treated with kinase inhibitors, suggesting that there is no cross resistance with other compounds. On the basis of these favorable results, a randomized phase III trial of cabozantinib (175 mg/day) versus placebo is ongoing in patients with progressive MTC (NCT00704730).

Motesanib. In a phase II trial, motesanib (starting at 125 mg/day) induced a partial response in only two of 91 patients, but another 43% had stable disease longer than 24 weeks. The low efficacy of the drug may be attributed to its malabsorption related to diarrhea (24).

Table 2 - Results obtained in patients with medullary thyroid carcinoma with kinase inhibitors.

	Author	Patients (n)	PR (%)	SD >6 months (%)	Median PFS (months)	Median OS (months)	Dose reduction for toxicity (%)	Withdrawal for toxicity (%)
Vandetanib	Wells (2010)	30	30/20 c	53	27.9	NE	73	23
	Robinson (2010)	19	16	NE	NE	10	15	11
	Wells (2010)	331	44	53	30.5 (v) *vs.* 19.3 (placebo)	>36	35	12
Cabozantinib	Kurzrock (2010)	34	50/29 c	44				
Motesanib	Schlumberger (2009)	83	2	43	11	NE	NE	NE
Axitinib	Cohen (2008)	11	18	27	17	>36	38	13
Sunitinib	De Souza (2010)	25	32	46	NE	NE	NE	
	Carr (2010)	6	50	33	NE	NE	NE	
Sorafenib	Kober (2007)	5	40	aaa	aaa	aaa	aaa	aaa
	Lam (2010)	19	10	43	17.9	NE	76	16
Pazopanib	Bible (2010)	14	7	57				
Imatinib	DeGroot (2007)	15	0	27			27	20
	Frank-Raue (2007)	9	0	56				

PFS = progression-free survival, OS = overall survival, c = confirmed; NE = not evaluated.

Sorafenib. In a phase II trial, sorafenib (400 mg/twice daily) induced a partial response in two of 21 patients, and another nine patients had stable disease for more than 15 months; calcitonin levels decreased over 50% in nine patients (25). In another trial with five MTC patients, two had a partial response (26). A phase I trial of sorafenib combined with the farnesyl transferase inhibitor tipifarnib yielded partial response in five patients and stable disease in another five patients, with a median PFS of 15 months (27).

Axitinib. In a phase II trial, axitinib (5 mg twice daily) induced a partial response in two of 11 patients and another three patients had stable disease lasting at least 16 weeks (28).

Sunitinib. In a phase II trial, sunitinib (50 mg/day, 4 weeks on and 2 weeks off) induced a partial response in eight of 25 patients and another 46% had disease stabilization for more than 24 weeks (29). In a smaller trial, sunitinib (37.5 mg/day continuously) induced a partial response in three of six patients (30).

Pazopanib. In a phase II trial, pazopanib (800 mg/day) induced a partial response in one of 14 patients and another eight patients had stable disease (31).

Lenvatinib (E7080). E7080 showed promising results in several MTC patients in a phase I trial (32), and a phase II trial in progressive MTC is ongoing (NCT00784303).

Imatinib. Imatinib was used in two trials (starting dose 600 mg/day) on nine and 15 MTC patients, respectively, and no tumor response was observed (33,34). In a phase I trial combining imatinib with dacarbazine and capecitabine, no response was observed in seven MTC patients (35).

Toxicities of molecularly targeted therapies

Adverse effects from these targeted therapies are significant, including fatigue, hypertension, QTc prolongation, anorexia, diarrhea, cytopenias, and skin toxicities. These short- or median-term side effects may lead to dose reduction in 11–73% of patients and to withdrawal of drug in 7–25%. Serum thyroid-stimulating hormone levels should be regularly monitored as they may increase during treatment with any of these kinase inhibitors; such an effect should lead to an increase in the daily levothyroxine treatment dose (36). Given that these treatment modalities may be given for months or even years, further work to minimize toxicities is needed.

CONCLUSION AND PERSPECTIVES

Although response criteria in contemporary trials differ markedly from those in trials evaluating cytotoxic chemotherapy, the anti-tumor efficacy of these agents in MTC patients is likely to be much greater than that of earlier chemotherapies. Benefits demonstrated with vandetanib in improving PFS and delaying worsening of pain counterbalance its adverse effects. Results of the ongoing phase III trial with cabozantinib are also expected to confirm the promising results obtained in the phase I trial. To date only vandetanib has been labeled by the US Food and Drug Administration for use in the rare MTC patients with a large tumor burden in whom progression has been documented, and it should be used as first-line treatment for this indication. Patients in whom the use of vandetanib is contraindicated or who experience toxicity or resistance should preferably be included in prospective trials, and even phase I trials that are testing the newest therapies should be considered for patients with progressive thyroid cancer, as these protocols may allow early identification of possibly effective drugs (37).

The drugs used up to now have similar mechanisms of action: all are anti-angiogenic and most also target the RET kinase. The relative role of the inhibition of each target or of their combined inhibition is currently unknown, but because axitinib and pazopanib are thought not to inhibit RET kinase, responses suggest an important role for the anti-angiogenic effects of these compounds. Also, responses to vandetanib or cabozantinib have been observed in patients without RET mutation, probably indicating that targeting mutant RET may not be necessary in all MTC tumors.

Future progress will be made in three directions. Firstly, by improving the knowledge of targets present in each individual tumor and by increasing the number of drugs directed against each of these targets, it may be possible to offer thyroid cancer patients a personalized selection of therapies. Secondly, there is an urgent need to test other drugs in thyroid cancer patients and to understand the basis of tumor response. Further trials should also search for other treatment modalities, including combination with cytotoxic chemotherapy or sequential treatment modalities or immunotherapy (21). Finally, to increase the accrual of patients, to optimize the experimental design of the protocol, to improve the characterization of tumor tissues, and to improve the tolerance of treatment, the collaborative participation of a multidisciplinary team of endocrinologists, oncologists, nuclear physicians, surgeons, pathologists, laboratory researchers, and statisticians should be strongly encouraged through national and international networks.

Search strategy: All papers written in English found on PubMed between 2000 and 2010 using the key words ''metastatic thyroid cancer, anaplastic thyroid cancer, targeted therapies'' were analyzed.

Conflicts of interest: MS: Amgen, Astra-Zeneca, Bayer, Exelixis, Eisai, Genzyme, Ipsen Pharma, Roche.

AUTHOR CONTRIBUTIONS

All authors were responsible for the writing and approval of the manuscript.

REFERENCES

1. American Thyroid Association Guidelines Task Force, Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid. 2009;19:565-612, http://dx.doi.org/10.1089/thy.2008.0403.
2. Schlumberger M, Carlomagno F, Baudin E, Bidart JM, Santoro M. New therapeutic approaches to treat medullary thyroid carcinoma. Nat Clin Pract Endocrinol Metab. 2008;4:22-32, http://dx.doi.org/10.1038/ncpendmet0717.
3. Giraudet AL, Vanel D, Leboulleux S, Aupérin A, Dromain C, Chami L, et al. Imaging medullary thyroid carcinoma with persistent elevated calcitonin levels. J Clin Endocrinol Metab. 2007;92:4185-90. Epub 2007 Aug 28, http://dx.doi.org/10.1210/jc.2007-1211
4. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47, http://dx.doi.org/10.1016/j.ejca.2008.10.026.
5. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer

Institute of Canada. J Natl Cancer Inst. 2000;92:205-16, http://dx.doi.org/10.1093/jnci/92.3.205.
6. Laure Giraudet A, Al Ghulzan A, Aupérin A, Leboulleux S, Chehboun A, Troalen F, et al. Progression of medullary thyroid carcinoma: assessment with calcitonin and carcinoembryonic antigen doubling times. Eur J Endocrinol. 2008;158:239-46, http://dx.doi.org/10.1530/EJE-07-0667.
7. Barbet J, Campion L, Kraeber-Bodere F, Chatal JF. Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. J Clin Endocrinol Metab. 2005;90:6077-84, http://dx.doi.org/10.1210/jc.2005-0044.
8. Shimaoka K, Schoenfeld DA, DeWys WD, Creech RH, DeConti R. A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. Cancer. 1985;56:2155-60, http://dx.doi.org/10.1002/1097-0142(19851101)56:9<2155::AID-CNCR2820560903>3.0.CO;2-E.
9. Williams SD, Birch R, Einhorn LH. Phase II evaluation of doxorubicin plus cisplatin in advanced thyroid cancer: a Southeastern Cancer Study Group Trial. Cancer Treat Rep. 1986;70:405-7.
10. Nocera M, Baudin E, Pellegriti G, Cailleux AF, Mechelany-Corone C, Schlumberger M, et al. Treatment of advanced medullary thyroid cancer with an alternating combination of doxorubicin-streptozocin and 5 FU-dacarbazine. Groupe d'Etude des Tumeurs a Calcitonine (GETC). Br J Cancer. 2000;83:715-8, http://dx.doi.org/10.1054/bjoc.2000.1314.
11. Kraeber-Bodere F, Goldenberg DM, Chatal JF, Barbet J. Pretargeted radioimmunotherapy in the treatment of metastatic medullary thyroid cancer. Curr Oncol. 2009;16:3-8.
12. Iten F, Müller B, Schindler C, Rochlitz C, Oertli D, Mäcke HR, et al. Response to [90Yttrium-DOTA]-TOC treatment is associated with long-term survival benefit in metastasized medullary thyroid cancer: a phase II clinical trial. Clin Cancer Res. 2007;13:6696-702, http://dx.doi.org/10.1158/1078-0432.CCR-07-0935.
13. Papewalis C, Wuttke M, Seissler J, Meyer Y, Kessler C, Jacobs B, et al. Dendritic cell vaccination with xenogenic polypeptide hormone induces tumor rejection in neuroendocrine cancer. Clin Cancer Res. 2008;14:4298-305, http://dx.doi.org/10.1158/1078-0432.CCR-08-0587.
14. Wells SA Jr, Santoro M. Targeting the RET pathway in thyroid cancer. Clin Cancer Res. 2009;15:7119-23, http://dx.doi.org/10.1158/1078-0432.CCR-08-2742.
15. Moura MM, Cavaco BM, Pinto AE, Leite V. High prevalence of RAS mutations in RET-negative sporadic medullary thyroid carcinomas. J Clin Endocrinol Metab. 2011;96:863-8, http://dx.doi.org/10.1210/jc.2010-1921.
16. Papotti M, Olivero M, Volante M, Negro F, Prat M, Comoglio PM, et al. Expression of hepatocyte growth factor (HGF) and its receptor (MET) in medullary carcinoma of the thyroid. Endocr Pathol. 2000;11:19-30, http://dx.doi.org/10.1385/EP:11:1:19.
17. Capp C, Wajner SM, Siqueira DR, Brasil BA, Meurer L, Maia AL. Increased expression of vascular endothelial growth factor and its receptors, VEGFR-1 and VEGFR-2, in medullary thyroid carcinoma. Thyroid. 2010;20:863-71, http://dx.doi.org/10.1089/thy.2009.0417.
18. Kurzrock R, Sherman SI, Ball DW, Forastiere AA, Cohen RB, Mehra R, et al. Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients With medullary thyroid cancer. J Clin Oncol. 2011;29:2660-6. Epub 2011 May 23, http://dx.doi.org/10.1200/JCO.2010.32.4145
19. Tuttle RM, Ball DW, Byrd D, Daniels GH, Dilawari RA, Doherty GM, et al. Medullary carcinoma. J Natl Compr Canc Netw. 2010;8:512-30.
20. Wells SA Jr, Gosnell JE, Gagel RF, Moley J, Pfister D, Sosa JA, et al. Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Oncol. 2010;28:767-72. Epub 2010 Jan 11, http://dx.doi.org/10.1200/JCO.2009.23.6604
21. Robinson BG, Paz-Ares L, Krebs A, Vasselli J, Haddad R. Vandetanib (100 mg) in patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Endocrinol Metab. 2010;95:2664-71. Epub 2010 Apr 6, http://dx.doi.org/10.1210/jc.2009-2461
22. Wells SA, Robinson BG, Gagel RF, Dralle H. Vandetanib (VAN) in locally advanced or metastatic medullary thyroid cancer (MTC): a randomized, double-blind phase III trial (ZETA). J Clin Oncol. 2010;28(15 Suppl):5503.
23. Akeno-Stuart N, Croyle M, Knauf JA, Malaguarnera R, Vitagliano D, Santoro M, et al. The RET kinase inhibitor NVP-AST487 blocks growth and calcitonin gene expression through distinct mechanisms in medullary thyroid cancer cells. Cancer Res. 2007;67:6956-64, http://dx.doi.org/10.1158/0008-5472.CAN-06-4605.
24. Schlumberger M, Elisei R, Bastholt L, Wirth LJ, Martins RG, Locati L, et al. Phase II study of safety and efficacy of motesanib (AMG 706) in patients with progressive or symptomatic, advanced or metastatic medullary thyroid cancer. J Clin Oncol. 2009;27:3794-801, http://dx.doi.org/10.1200/JCO.2008.18.7815.
25. Lam ET, Ringel MD, Kloos RT, Prior TW, Knopp MV, Liang J, et al. Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer. J Clin Oncol. 2010;28:2323-30, http://dx.doi.org/10.1200/JCO.2009.25.0068.
26. Kober F, Hermann M, Handler A, Krotla G. Effect of sorafenib in symptomatic metastatic medullary thyroid cancer. J Clin Oncol. 2007;25(18 Suppl):14065.
27. Cabanillas ME, Kurzrock R, Sherman SI, Tsimberidou AM, Waguespack S, Naing AN, et al. Phase I trial of combination sorafenib and tipifarnib: the experience in advanced differentiated thyroid cancer (DTC) and medullary thyroid cancer (MTC). J Clin Oncol. 2010;28(15 Suppl):5586.
28. Cohen EE, Rosen LS, Vokes EE, Kies MS, Forastiere AA, Worden FP, et al. Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. J Clin Oncol. 2008;26:4708-13, http://dx.doi.org/10.1200/JCO.2007.15.9566.
29. Lam ET, Ringel MD, Kloos RT, Prior TW, Knopp MV, Liang J, et al. Phase II trial of sunitinib in medullary thyroid cancer (MTC). J Clin Oncol. 2008;26:4708-13. Epub 2008 Jun 9, http://dx.doi.org/10.1200/JCO.2007.15.9566
30. Carr LL, Mankoff DA, Goulart BH, Eaton KD, Capell PT, Kell EM, et al. Phase II study of daily sunitinib in FDG-PET-positive, iodine-refractory differentiated thyroid cancer and metastatic medullary carcinoma of the thyroid with functional imaging correlation. Clin Cancer Res. 2010;16:5260-8. Epub 2010 Sep 16, http://dx.doi.org/10.1158/1078-0432.CCR-10-0994
31. Bible KC. Phase II trial of pazopanib in rapidly progressive, metastatic, medullary thyroid cancer. Thyroid (Meeting Abstracts). 2009;19:S110.
32. Mross K, Frost A, Steinbild S, Hedbom S, Rentschler J, Kaiser R, et al. Phase I dose-escalation study of E7080, a multikinase inhibitor, in patients with advanced solid tumors. J Clin Oncol. 2008;26:5511-7. Epub 2008 Oct 27, http://dx.doi.org/10.1200/JCO.2008.16.1547.
33. Frank-Raue K, Fabel M, Delorme S, Haberkorn U, Raue F. Efficacy of imatinib mesylate in advanced medullary thyroid carcinoma. Eur J Endocrinol. 2007;157:215-20, http://dx.doi.org/10.1530/EJE-06-0695.
34. de Groot JW, Zonnenberg BA, van Ufford-Mannesse PQ, de Vries MM, Links TP, Lips CJ, et al. A phase-II trial of imatinib therapy for metastatic medullary thyroid carcinoma. J Clin Endocrinol Metab. 2007;92:3466-9, http://dx.doi.org/10.1210/jc.2007-0649.
35. Hoff PM, Hoff AO, Phanet AT, Sherman SI, Yao J, White N, et al. Phase I/II trial of capecitabine (C), dacarbazine (D) and imatinib (I) (CDI) for patients (pts) metastatic medullary thyroid carcinomas (MTC). J Clin Oncol. 2006;24(18 Suppl):13048.
36. Abdulrahman RM, Verloop H, Hoftijzer H, Verburg E, Hovens GC, Corssmit EP, et al. Sorafenib-induced hypothyroidism is associated with increased type 3 deiodination. J Clin Endocrinol Metab. 2010;95:3758-62, http://dx.doi.org/10.1210/jc.2009-2507.
37. Tsimberidou AM, Vaklavas C, Wen S, Hong D, Wheler J, Ng C, et al. Phase I clinical trials in 56 patients with thyroid cancer: the M. D. Anderson Cancer Center experience. J Clin Endocrinol Metab. 2009;94:4423-32, http://dx.doi.org/10.1210/jc.2009-0743.